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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,308	01/02/2002	Hugo A.G. Geerts	JAB-1515	8790

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Philip S Johnson
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003

EXAMINER	
BERTOGLIO, VALARIE E	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 02/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,308	GEERTS ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44 and 49-51* is/are pending in the application.

4a) Of the above claim(s) *12-19,24-44 and 49-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) *6-9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01/02/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 12/30/2003 has been entered. Claim 43 has been amended. Claims 1-44 and 49-51 are pending and claims 1-11 and 20-23 are under consideration in the instant action.

Election/Restrictions

Claims 12-19, 24-44 and 49-51 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the election dated 12/30/2003.

Revised amendment practice

The amendment to the claims filed with the amendment filed 12/30/2003 is not compliant with the revised amendment practice. Each section of an amendment document should begin on a separate page. Non-elected claims should be marked as 'withdrawn'. Refer to 37 CFR 1.121.

Claim Objections

Claims 6-9 and 20 are objected to because of the following informalities:

Claims 6-9 are objected to under 37 CFR 1.75(c) as being in improper form because the claims are dependent claims, however do not specify a parent claim. A claim number has been omitted from the body of claim 6. See MPEP § 608.01(n). Claim 20 is objected to because it depends from a non-elected claim.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 20 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 20 encompasses on human cells in vivo and therefor reads on a human being. A human being is non-statutory subject matter. See 1077 O.G. 24, April 21, 1987.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 and 20-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) a nucleic acid vector comprising a nucleic acid sequence encoding a human Tau protein and a sequence capable of directing expression of said human Tau nucleic acid in the nervous system wherein the sequence capable of directing expression is the Thy1 promoter and wherein the vector is capable of integrating into the endogenous Tau equivalent gene of a mouse and for 2) an in vitro isolated, pluripotent or lineage restricted host cell transformed, transfected or injected with a claimed vector, does not reasonably provide enablement for any sequence capable of directing expression of said human Tau nucleic acid in the nervous system or a vector wherein said vector can integrate into the

genome of any species of non-human animal and integration of said vector prevents expression of the endogenous Tau equivalent gene or 2) a cell in vivo or any totipotent cell comprising the claimed vector. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The breadth of claims 1-11 encompasses a nucleic acid vector comprising a nucleic acid encoding human Tau operably linked to any promoter that drives gene expression in the nervous system of a non-human animal. Claims 1-11 further encompass a targeting sequence that facilitates integration of the vector into the genome of any species of non-human animal (claim 1, step c). Claim 1 includes the limitation that the "equivalent Tau protein" of the animal is not expressed (claim1, step c). Claims 20-23 encompass cells in vivo and in vitro and further encompass totipotent cells as well as pluripotent and lineage restricted cells.

The specification fails to enable the breadth of the claims as they relate to the use of the claimed nucleic acid vector to make a transgenic non-human animal and to cells, including the vector 1) wherein said vector comprises any promoter, 2) wherein integration of the vector into the genome of an animal prevents expression of the "equivalent Tau protein" (claim 1, step c) and 3) wherein said vector comprises a targeting sequence which facilitates integration of said vector into the genome of an animal. The specification teaches using the claimed nucleic acid vector wherein the vector comprises the Thy-1 promoter and wherein the nucleic acid is targeted to the endogenous Tau gene of a mouse. The specification does not teach using any promoter of any animal species and does not teach that integration of the claimed vector prevents endogenous

Tau expression (page 28, lines 16-22). Furthermore, the specification does not teach integrating the claimed vector into the genome of any species of non-human animal other than mouse.

The state of the art at the time of filing was such that one of skill could not predict the phenotype of transgenics, in part due to the unpredictability of promoter activity in various species of animal. The elements of the particular construct used to make transgenic animals are held to be critical, and they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (Houdebine, 1994, J. Biotech. Vol. 34, pages 269-287, specifically page 273-276). Examples in the literature aptly demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. Mullins (1993, Hypertension, Vol. 22, pp. 630-633) states that not all animals express a transgene sufficiently to provide a model for a disease as the integration of a transgene into different species of animal has been reported to give divergent phenotypes. Mullins (1996, J. Clin. Invest. Vol. 98, pages S37-S40) disclose that the use of nonmurine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another. Therefore, the art at the time of filing held that the activity of any given promoter in various species of animal was unpredictable and the phenotype caused by a transgene in a transgenic animal comprising any given promoter is also unpredictable.

The specification discloses that the use of the claimed nucleic acid vector is in generating a non-human animal wherein the endogenous Tau gene is replaced by the human Tau gene (see sentence bridging pages 2-3). The specification does not teach how to use the vector wherein

expression of the human Tau gene is directed by any sequence capable of directing expression in the nervous system. The specification fails to provide any correlation of the activity of the Thy-1 promoter in mouse to the activity of any other nervous system promoter encompassed by the claims. As set forth by the art at the time of filing, the phenotype of transgenic animals is highly unpredictable and it is not clear that expression of the claimed human Tau gene anywhere in the nervous system using any promoter would lead to a phenotype in a non-human animal that would be useful or to any phenotype at all. In so much as one of skill in the art would not know how to use a transgenic animal that does not have a phenotype, one of skill in the art would not know how to use the claimed nucleic acid. Therefore, as the specification teaches using the Thy1 promoter to drive expression to the nervous system of a mouse and use of the mouse to cause Tau hyper-phosphorylation associated with Alzheimer's disease, the specification is enabling only for the claimed nucleic acid wherein the human Tau gene is operably linked to the Thy1 promoter. The specification fails to overcome unpredictability of promoter activity as set forth by the art so as to provide the guidance necessary for one of skill in the art to use the claimed nucleic acid comprising any promoter capable of driving expression of human Tau in the nervous system of a non-human animal.

With respect to the limitation of claim 1 wherein the integration of the vector into the genome of an animal prevents expression of equivalent Tau protein, the specification only teaches the claimed vector wherein mice having said vector integrated into the genome fails to prevent expression of the equivalent Tau protein of the animal (page 28, lines 16-22). The specification does not teach the claimed vector wherein expression of the endogenous Tau equivalent is prevented. The specification fails to provide the guidance necessary to make the

claimed nucleic acid such that integration of said vector into the genome of an animal will prevent expression of the human Tau gene equivalent. The specification further fails to teach that the claimed nucleic acid that does not prevent endogenous Tau expression will result in a phenotype in a non-human animal and how to use said non-human animal.

With further respect to claims 1-11, the claims encompass integrating the claimed vector into the genome of any species of non-human animal. Generation of transgenic animals using homologous recombination requires the use of totipotent ES cells. To generate a non-chimeric animal from the recombinant ES cells, the cells must be capable of contributing to the germ line. Campbell and Wilmut (1997, Theriogenology, vol. 47, pp, 63-72) acknowledge reports of ES-like cells in a number of species, but emphasize that as yet there are no reports of any cell lines that contribute to the germ line in any species other than mouse (page 65). ES cell technology is generally limited to the mouse system at present, and that only "putative", pluripotent ES cells exist for other species (see Moreadith et al., J. Mol. Med., 1997, p. 214, Summary). Note that "putative" ES cells lack a demonstration of the cell to give rise to germline tissue or the whole animal, a demonstration that is an art-recognized property of ES cells. This is further supported by Pera et al. [2000, Journal of Cell Science, Vol. 113, pages 5-10] who present the generic criteria for pluripotent ES or EG cells [see p. 6, 2nd column] and state that, "Thus far, only mouse EG or ES cells meet these generic criteria. Primate ES cells meet the first three of the four criteria, but not the last. Numerous other candidate mammalian ES cells have been described over the years in domestic and laboratory species, but only in the mouse have all criteria been met rigorously." [See p. 6, 2nd column, last ¶]. Thus, the specification fails to overcome the

underdeveloped nature of the art as it relates to totipotent ES cells in that it fails to provide the guidance necessary to generate totipotent ES cells from non-mouse species.

For the same reasons, the specification fails to provide teachings or guidance for the totipotent cells encompassed by claims 20-23. The claims broadly encompass any cell type in vivo, including totipotent cells. As set forth above, it would require undue experimentation for one of skill in the art to make the totipotent cells encompassed by the claims and therefore would also fail to enable using the claimed nucleic acid (claims 1-11) to generate any species of animal comprising the nucleic acid as well as the cells broadly encompassed by the claims (claims 20-23).

Thus, for the reasons given above, it would require undue experimentation for one of skill in the art at the time of filing use the invention as claimed with a predictable degree of success. There is insufficient guidance in the specification, in view of the state of the art at the time of filing, to determine that broadly claimed nucleic acid would have the claimed effect of preventing endogenous Tau expression and cause Tau-hyperphosphorylation in the broad number of animal species encompassed by the claims. There is also insufficient guidance in the specification to overcome the underdeveloped nature of the art of ES cell technology to enable one of skill in the art to make and use the totipotent cells encompassed by the claims.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites, in step b, "a sequence capable of directing expression of said human Tau protein". This is unclear because genes are expressed, while proteins are the products of gene expression. Claims 2-11 depend from claim 1 and are included in this rejection.

Claim 22 is unclear because it is not known what is meant by the phrase "embryo cell". The specification fails to define what an "embryo cell" is. For purposes of examination the phrase has been interpreted as an embryonic cell.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Fri 6:00-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

PETER PARAS
PATENT EXAMINER

Valarie Bertoglio
Examiner
Art Unit 1632